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Allergic rhinitis: not purely a histamine-related disease

Allergic rhinitis is an inflammatory disorder of the nasal mucosa typified by the symptoms of nasal itch, sneeze, anterior nasal secretions, and nasal blockage. These symptoms arise from the interaction between mediators and neural, vascular, and glandular structures within the nose. Nasal itch, sneezes, and rhinorrhoea are predominantly neural in origin, while nasal obstruction is predominantly vascular. Nasal biopsy studies show accumulation of eosinophils within the lamina propria and epithelium and an increase in tissue and cell surface basophils in both seasonal and perennial allergic rhinitis. These cells are in an activated state. Within the epithelium, increased numbers of mast cells, T cells and Langerhans' cells, which induce T-cell activation, are found. The accumulation of these cells can be linked to chemokine and cytokine generation by the epithelial cells themselves. Thus, the tissue cell recruitment is orchestrated by activated mast cells, T cells, and epithelial cells, with the recruited tissue eosinophils also contributing to their persistence at this site through autocrine mechanisms. Mast cells generate an array of mediators including histamine, tryptase, leukotrienes, and prostaglandins. Histamine is also generated by basophils. Eosinophils and basophils contribute to the leukotriene synthesis within the tissue. Histamine nasal insufflation induces nasal itch, sneeze, and rhinorrhoea as well as nasal blockage, thereby reproducing all the symptoms of allergic rhinitis. These effects are primarily mediated by H_1-receptors, and H_1-receptor antagonists are a prominent treatment. Antagonism of histamine at these receptors reduces symptoms by about 40–50%, with the greatest effect on the neurally mediated responses. Thus, histamine is a major mediator of allergic rhinitis, but not the sole contributor. Nasal insufflation with leukotrienes, prostaglandins, or kinins is associated with the development of nasal blockage. These mediators act primarily on the nasal vasculature and, in this respect, leukotrienes are potent mediators. Leukotrienes also induce plasma protein exudation, which contributes to the anterior nasal secretions. Studies with combination products have suggested that modifying the effects of both leukotrienes and histamine has complementary effects in relieving nasal symptoms, indicating that both these mediators are relevant to disease expression.

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Introduction

Allergic rhinitis is an inflammatory condition of the nasal mucosa that arises on account of an allergen–IgE interaction in sensitized individuals and is characterized typically by the clinical symptoms of nasal itch, bouts of sneezing, nose running, and nasal congestion, giving rise to difficulty in breathing through the nose (1). Nasal biopsies reveal an accumulation of mast cells, eosinophils, and basophils within the airway epithelium in individuals with active disease in addition to eosinophil accumulation within the deeper lamina propria (2–4).

Symptom generation

The accumulated cells are in an activated state, and it is the mediators released by the cells that lead to the symptom generation through stimulating specific receptors on sensory nerves and blood vessels within the nasal mucosa (5). Stimulation of sensory nerves leads to the sensation of itch, sneezing, and, via reflex stimulation of efferent vagal pathways, glandular secretion and hence anterior rhinorrhoea (Fig. 1). In addition, the local release of neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP), from non-adrenergic noncholinergic nerves within the nasal mucosa can modify the state of nasal vascular engorgement, either through a direct action on the vessels, promoting vasodilatation, or indirectly by modifying sympathetic ganglionic neurotransmission. The nasal vasculature is under sympathetic tone; the sympathetic neurotransmitter, noradrenaline, promotes vasoconstriction and maintains nasal airway patency. The ganglionic reduction in sympathetic tone by

neuropeptides will thus lead indirectly to nasal congestion. In addition to these neural effects, mediators generated from mast cells, basophils, and eosinophils, such as histamine, tryptase, kinins, prostaglandins (PGs), and leukotrienes (LTs), have direct effects on the nasal vasculature through their interaction with specific receptors.

The nasal vascular anatomy is complex and includes both resistance and capacitance vessels (6). The resistance vessels are predominantly small arteries, arterioles, and arteriovenous anastamoses. These vessels are fed by the anterior and posterior ethmoid arteries, and flow through these vessels is regulated under normal circumstances by sympathetic tone. Arterial blood reaches the venous drainage system, either via superficial capillaries or via arteriovenous anastomoses (Fig. 2).

The superficial capillaries beneath the basement membrane and around the glandular tissue are unusual in being fenestrated, with the fenestrations facing the respiratory epithelium. This fenestration allows unimpeded extravasation of plasma proteins. The fenestrations – holes in the vascular basement membrane that are not covered by endothelial cells – indicate that plasma extravasation is an important intrinsic property of the vessels at this site. Extravasated plasma contains albumin and immunoglobulins, as well as factors involved in the kinin, complement, coagulation, and fibrinolytic systems (7). It is probable that this exudation is essential both for epithelial nutrition and for local immune defence. In contrast to vascular exudation at most other sites, which occurs via gaps in endothelial cells at postcapillary venules and is dependent upon endothelial cell behaviour, the predominant determinant of exudation at this site is arteriolar tone. Arteriolar dilatation promotes exudation, by increasing capillary blood flow and increasing capillary vascular pressure. The balance between arteriovenous anastomotic flow and capillary flow determines the magnitude of exudation. Plasma protein exudation is an important hallmark of the airway inflammation in allergic rhinitis (8).

The arterial blood drains into a venous system composed of a labyrinth of valveless venous sinusoids within the lamina propria that are particularly prominent within the turbinates. The large collapsible venous sinusoids form the capacitance components of the system. Vascular congestion of the venous sinusoid results in engorgement of the turbinates, an increase in nasal airways resistance, and a reduction in nasal airflow. The venous engorgement is under sympathetic regulation and is determined by the tone of the arteriolar, arteriovenous, anastomotic, and muscular venous draining vessels. Nasal blockage and plasma protein exudation are thus reflections of the vascular changes associated with nasal allergy. Many mediators influence this vasculature including histamine, LTs, PGs, and kinins (9).

IgE and rhinitis

The basis for the development of allergic rhinitis is the overexpression of IgE and the interaction of IgE and allergen. A significant relationship has been demonstrated in community epidemiological studies between the level of specific IgE in the serum and the likelihood of expressing clinical rhinitis (10). The nature of the rhinitis depends upon the sensitization, with specific pollen-related IgE against trees, grasses, or weeds giving rise to seasonal-related symptoms, and that against the common indoor allergens, such as those related to house-dust mites, pets, or cockroaches, often leading to perennial disease.

IgE is generated by B cells under the regulation of cytokines generated by T cells. This is determined by key cytokines, such as interleukin (IL)-4 (11) and IL-13 (12), in addition to copromoting cytokines such as IL-6 and specific receptor-ligand interactions that occur during cell-to-cell contact between the two populations of lymphocytes. These signalling interactions involve cognate interactions between B-cell MHC class II and the T-cell receptor/CD3 complex (13), as well as noncognate interactions, involving B-cell-expressed CD40 and its complementary ligand, expressed as activated T cells (14), and between B7-1 and B7-2 and the CD28 receptor (15), also expressed on the T-cell surface. These interactions and B-cell IgE synthesis are primarily considered to take place in draining lymph nodes, with the antigen having been presented to T cells in a modified format by antigen-presenting cells within the nasal mucosa.

At this site, it is the Langerhans' or dendritic cell that appears to be the most capable antigen-presenting cell (16). Immunohistochemical staining of nasal mucosal biopsies has confirmed the presence of these cells and has demonstrated that they increase in number in naturally occurring seasonal allergic rhinitis (17), as well as following repeated laboratory allergen challenge out of season (18). In addition to this, there is now evidence, at least following allergen challenge in the laboratory, that there may be local IgE generation within the nasal mucosa (19). *In situ* hybridization studies have identified increased mRNA expression for the heavy chain for IgE that can be localized to B cells within nasal biopsies taken 24 h after nasal allergen challenge. In the same study, the challenge was associated with increased mRNA expression for IL-4, which was localized predominantly to tissue T cells and to mast cells. Both of these cell populations could thus be linked to this local IgE generation, as, in addition to the described T-cell interactions with B cells, mast cells have been shown to express the CD40 ligand (20), and *in vitro*, in the presence of IL-4, stimulation of CD40 on the B-cell surface can promote IgE synthesis (21). The local generation of IgE provides a ready mechanism for IgE availability to bind to tissue cells. Immunohistochemical

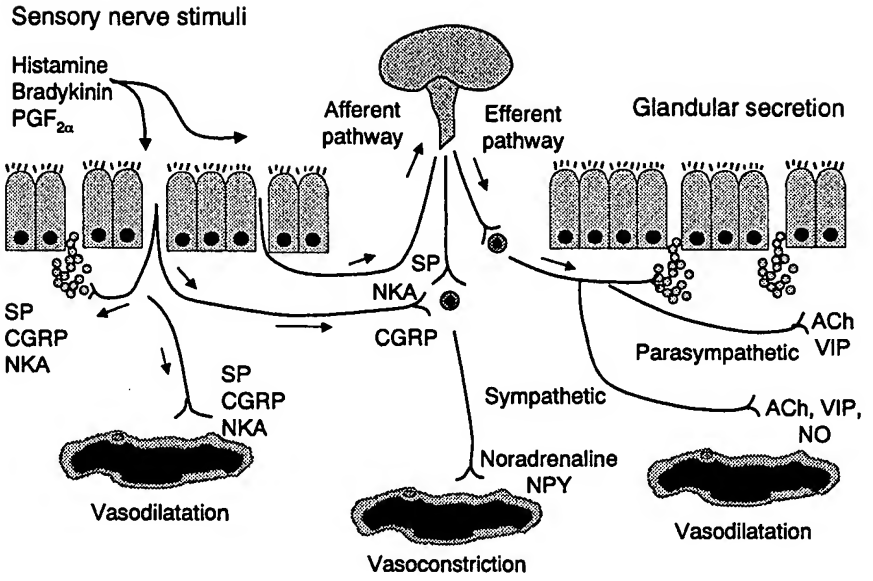

Figure 1. Schematic representation of afferent and efferent neural stimulatory pathways involved in regulation of glandular secretion and nasal vascular volume. $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$; SP: substance P; CGRP: calcitonin-gene-related peptide; NKA: neurokinin A; NPY: neuropeptide Y; ACh: acetylcholine; VIP: vasoactive intestinal polypeptide; NO: nitric oxide.

assessment of IgE localization within nasal mucosal biopsies reveals that, while it is present in several cell populations, most of it is colocalized to tissue mast cells.

Cellular basis of allergic rhinitis

Nasal biopsy studies reveal activation of a range of cell populations, involving both infiltrating cells and resident tissue cells (Fig. 3). The initial response to the allergen involves activation of immune cells. In this respect, Langerhans' cells, which present antigen to the T cell; the T cell itself; and the mast cell are all important orchestrators of the subsequent cellular response, through their ability to be activated by allergen and to release cytokines that modify the activity of other cell populations. Within the tissue, the epithelial cells and endothelial cells become activated and are involved in the recruitment of cells, such as eosinophils and basophils, from the circulation and their specific accumulation within the epithelium, along with mast

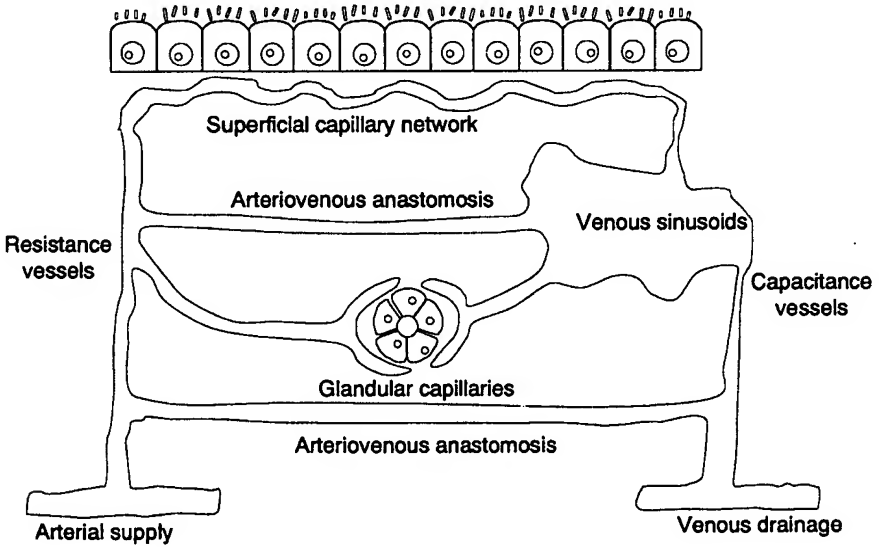

Figure 2. Schematic representation of nasal vasculature, illustrating links between arterial supply and venous drainage and positioning of venous capacitance vessels, whose state of engorgement within the turbinates is determinant of nasal airflow.

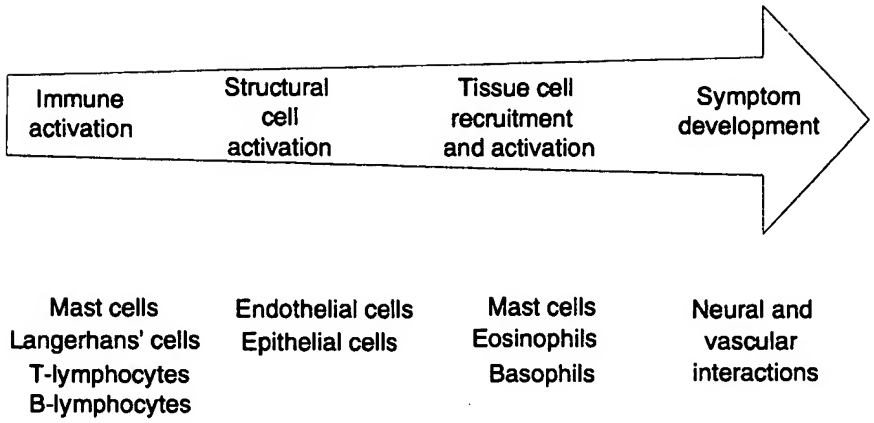

Figure 3. Schematic representation of cellular involvement and sequence underlying clinical disease expression in rhinitis.

cells and T cells. The endothelial activation is associated with the upregulation of leukocyte endothelial adhesion molecules, which are involved in the recruitment of the circulating cells. The epithelium can generate a range of products, but specifically the synthesis and release of chemokines, which are involved in the attraction and activation of cells to this site, represent an important process in allergic mucosal inflammation. Our understanding of the sequence of events and the cellular processes has come both from laboratory allergen challenge studies and from studies in naturally occurring disease. It appears that the initial response to allergen represents mast-cell activation due to cross-linkage of IgE, which is bound to the cell surface of mast cells, a process that leads to mast-cell degranulation.

Mast cells

Sequential nasal lavage following nasal allergen challenge in allergic rhinitis identifies the local release of histamine, tryptase, PGD_2, LTB_4, and LTC_4 in association with development of nasal pruritus, sneezing, rhinorrhoea, and nasal blockage (22–26). The increase in these mediators is rapid, peaking within 10–15 min of allergen exposure. Although histamine, LTB_4, and LTC_4 are not specific markers of mast-cell activation, the parallel identification of elevations in tryptase and PGD_2 is indicative of a mast-cell source and is consistent with mast-cell degranulation. In addition to these mediators, elevations in lavage levels of the kinins, kallidin (lysyl-bradykinin), and bradykinin have been reported (24). Kallidin and bradykinin are potent vasoactive peptides, formed as cleavage products from the action of kallikrein on low- and high-molecular-weight kininogens, respectively. The mast-cell protease tryptase possesses kallikrein-like activity and could thus contribute to the kinin generation identified under such circumstances.

Evidence exists for mast-cell activation and changes in mast-cell populations within the nasal mucosa during naturally occurring allergic rhinitis. Mast cells are constitutive cells of the normal nasal mucosa, but are not normally found superficially within the airway epithelium. Immunohistochemical staining of nasal biopsies with monoclonal antibodies against mast-cell tryptase identifies an increase in mast cells within the airway epithelium in both seasonal and perennial allergic rhinitis, in comparison with biopsy findings in nonatopic, nonrhinitic subjects (3, 4). The activation of these cells is suggested by the identification of elevated levels of the mast-cell mediator tryptase in nasal lavage fluid in both seasonal and perennial allergic disease (27), along with the identification of ultrastructural changes of degranulation on electron microscopic examination of nasal biopsies (28).

In addition to the mediators identified in naturally occurring disease, clear increases in LT levels in nasal lavage fluid also occur (29, 30). These LTs, which are generated from arachidonic acid (Fig. 4), may be

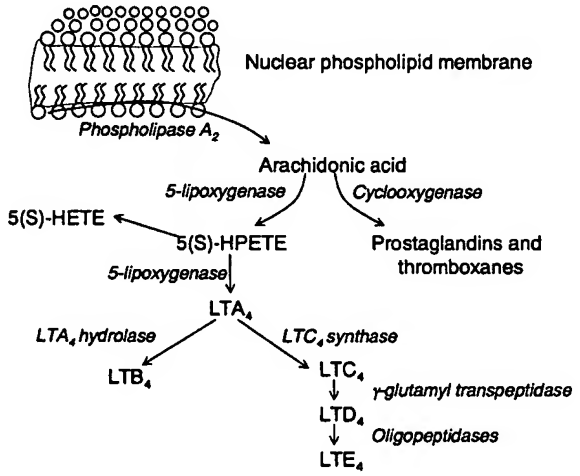

Figure 4. Biochemical pathway for the generation of sulphidopeptide leukotrienes by 5-lipoxygenase pathway in rhinitis.

derived from a variety of cell sources including eosinophils and basophils, in addition to mast cells (31). The release of cytokines from mast cells and from T cells will influence the recruitment of these leukocytes through their activation of endothelial and epithelial cells in addition to any systemic activity on the bone-marrow precursors.

T cells

The T cell represents a significant nonstructural infiltrating cell within the nasal mucosa and an epithelial accumulation in $CD4^+$ T cells has been described in rhinitis in both seasonal (32–34) and perennial disease (32, 35). Within perennial (36), but not seasonal (32), disease, increased cell-surface expression on T cells of the activation marker CD25 also occurs. This is associated with an increase in the number of IL-4-, IL-5-, and IL-13-positive cells, indicative of an increase in Th2 cytokine generation, particularly in perennial allergic disease (37, 38). *Ex vivo* studies have identified that the T cells expressing the γδ T-cell receptor, which specifically increase within the epithelial compartment in perennial allergic rhinitis, are the subpopulation of T cells that generate the Th2 cytokines in allergic as opposed to infective rhinitis (39).

Tissue and luminal cell recruitment: involvement of structural cells

Cytokines generated by mast cells and T cells can initiate the process of leukocyte tissue-cell recruitment. This involves endothelial cell activation, and the adherence, activation, and transendothelial migration of leukocytes, particularly eosinophils, but also basophils and T cells, and their subsequent migration under a chemotactic stimulus toward the epithelium. Activation of the epithelium and chemokine release from these cells can be implicated in this process.

Endothelial activation is an early event in the recruitment of circulating cells (40). The initial aspect of this process is the histamine-related upregulation of the selectin, P-selectin, on the endothelial surface that, along with the cytokine-upregulated E-selectin, induces a rolling margination. This brings the leukocytes into contact with chemokines, such as RANTES (released and normally T-cell expressed and secreted), macrophage inflammatory protein (MIP)-1α, and IL-8, presented on the endothelial glycocalyx, and activates these cells. Activation results in upregulated expression or functional conformational changes in cell-surface-expressed ligands, such as the β2 integrins. These integrins recognize specific ligands that allow firm adherence to the endothelial surface. In this respect, the expression of the β2-integrin, very late antigen 4 (VLA-4), by eosinophils, basophils, and T cells, but not neutrophils, confers some specificity in the recruitment, as Th2 cytokines, such as IL-4, IL-5, IL-13, and TNF-α, upregulate the leukocyte endothelial cell adhesion molecule VCAM-1 (vascular endothelial cell adhesion molecule 1), which provides firm adherence through its interaction with VLA-4. Endothelial VCAM-1 is overexpressed in rhinitis (41, 42), and its presence can be related to the number of infiltrating eosinophils and T cells (41, 43, 44).

The epithelium forms an interface between the internal and external environment, and these lining cells are activated in rhinitis. There is increased expression of the epithelially expressed intercellular adhesion molecule (ICAM-1) in naturally occurring seasonal rhinitis in both nasal smear and nasal biopsy samples (45, 46). Cultured human airways epithelial cells have been shown to synthesize granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, IL-8, and RANTES (47, 48), and the presence of enhanced IL-6, tumour necrosis factor (TNF)-α, IL-8, GM-CSF, and RANTES immunoreactivity has been demonstrated within the airway epithelium in nasal biopsies taken from individuals with perennial allergic rhinitis (49, 50). This activation is also indirectly reflected by the identification of elevated levels of nitric oxide (NO) in nasal luminal air in seasonal and perennial allergic rhinitis (51, 52). NO is generated by nitric oxide synthase (NOS) from the semi-essential amino acid L-arginine, and we and others have found evidence of increased epithelial expression of the inducible form of NOS (iNOS) in allergic airways disease (53). The increased generation of chemokines by the nasal airway epithelium can account for the cell recruitment to this site and to the nasal airway lumen (Fig. 5).

RANTES is expressed by epithelial cells and its generation is increased in atopic rhinitis (54). This chemokine has been implicated in mast-cell, basophil, eosinophil, and T-cell recruitment (55, 56); indeed, this has been confirmed *in vivo*, as nasal challenge with RANTES induces the tissue accumulation of basophils, eosinophils, and T cells (57). Another C-C (with two adjacent cysteine residues) chemokine, eotaxin, is also released by epithelial cells and is probably a key eosinophilic chemokine (58). Eotaxin mRNA is upregulated in the nasal tissue of patients with acute allergic rhinitis (59), and nasal challenge with eotaxin has been found to induce nasal eosinophilic inflammation. Another chemokine, monocyte chemotactic protein (MCP-1), also from the same subclass, may be generated from macrophages and is present within the nasal mucosa (60). It is also overexpressed in seasonal allergic rhinitis (61). This chemokine can activate monocytes and basophils, and is also implicated in eosinophil, T-cell, and monocyte cell influx and accumulation (62). The survival of cells at this site, particularly eosinophils and mast cells, is promoted by the respective epithelial generation of GM-CSF and stem-cell factor (SCF). Cultured nasal epithelial cells have been shown to

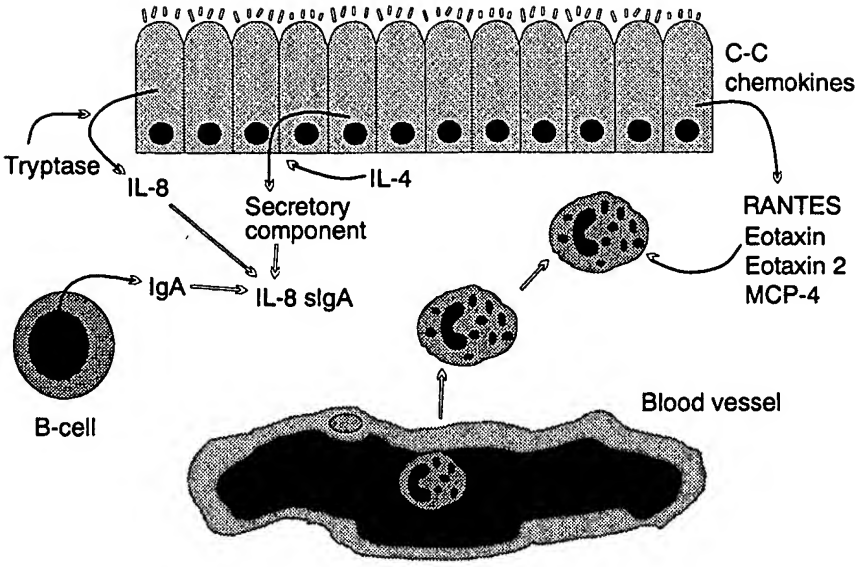

Figure 5. Epithelial chemokine generation and its relevance to nasal eosinophil accumulation. Interleukin-8 secretion IgA (IL-8sIgA) complex and RANTES, eotaxin, eotaxin 2, and monocyte chemotactic protein 4 (MCP-4) are all eosinophil chemoattractants. C-C: chemokines of C-C class; IL: interleukin.

generate SCF *in vitro*, and elevated levels of SCF have been found to be present in nasal lavage fluid in seasonal allergic rhinitis (63). The SCF levels correlated with nasal lavage mast-cell chemotactic activity. In support of this, a further study reported that SCF mRNA expression correlated with both mast-cell numbers and histamine content within the nasal mucosa (64).

TNF-α is an important cytokine regulating epithelial cell activation and is generated by mast cells and T cells. In addition, it is now apparent that allergens, which in themselves are also proteolytic enzymes, can directly activate epithelial cells independently of IgE (65) and lead to cytokine release (66). This process is enhanced by the local generation of the proteases, tryptase and chymase, released in association with mast-cell activation (65) and by the corelease of IL-4 and IL-13 from these cells, as these Th2 cytokines have recently been shown to upregulate epithelial cell activation (67).

The upregulated events involved in allergic airways inflammation are regulated by transcription factors. A number of different transcription factors are involved, but nuclear factor kappa B (NFκB) appears to be critical. It potentially regulates many products of relevance (68) and is pertinent to the regulation of the endothelial expression of adhesion molecules, such as E-selectin, ICAM-1, and VCAM-1; of chemokines, such as RANTES, eotaxin, MCP-1, TNF-α, and GM-CSF; and of enzymes, such as iNOS, which is involved in NO generation, and 5-lipoxygenase, which is involved in LT synthesis. NFκB probably functions in tandem with other transcription factors, such as AP-1 and C/EBP, which also control similar genes (69).

Infiltrating leukocytes

Nasal biopsies taken from the normal nose or from monoallergic pollen-sensitive subjects outside the pollen season reveal no evidence of eosinophilic airway inflammation, and nasal smears reveal very few if any basophils in these circumstances. The appearance of these cells within the nasal mucosal tissue and within nasal luminal samples is associated with clinical disease expression. Activation of these cells leads to mediator release, and it is probable that they contribute, along with mast-cell-derived mediators, to the severity of symptom expression.

Eosinophils

The presence of eosinophils within nasal samples, whether from nasal biopsies, nasal smears, or nasal lavage samples, is a feature of allergic nasal disease (70). The eosinophilia may be more marked in seasonal than perennial disease. These eosinophils are activated, as reflected by elevated levels of eosinophil cationic protein (ECP) in nasal lavage. Increased levels of ECP are evident in both seasonal and perennial allergic rhinitis in comparison to the normal nose (27). Eosinophils can also generate a range of other mediators, including LTs, cytokines, chemokines, and growth factors. The generation of IL-5 and eotaxin by these cells may serve an autocrine function. The generation of LTs from eosinophils is likely to contribute to plasma protein exudation, mucus hypersecretion, and nasal blockage.

Basophils

Circulating basophil and eosinophil progenitors are evident in peripheral blood in association with allergic rhinitis (71). These cells are derived from CD34+ progenitor cells within the bone marrow (72). Until recently, the lack of a good monoclonal antibody specific for basophils has hampered assessment of tissue accumulation of basophils, and their identification has largely depended upon ultrastructural evaluation of cells in nasal smear or lavage by transmission electronmicroscopy. There have been reports of basophils increasing within smear samples in active rhinitis (73, 74). Using a recently developed monoclonal antibody designated BB1 (Dr A. Walls, University of Southampton, UK), we have been able to immunostain nasal biopsy sections from normal nonrhinitic subjects and from those with seasonal and perennial allergic rhinitis. The number of basophils within tissue samples is small (median 4–5 cells/mm^2) in rhinitis in comparison to mast-cell numbers (median 30–40 cells/mm^2), but is significantly increased in both seasonal and perennial disease in comparison to the normal nose (median <1 cell/mm^2).

Basophils generate histamine and LTs on activation and are thus another potential cell contributor to the mediators of symptom expression in rhinitis. Supportive of this is the report that nasal smear basophil numbers in rhinitis correlate positively with the severity of the disease (75).

Mediators and symptom expression

Thus, the symptom expression in rhinitis is based on sensory neural stimulation giving rise to nasal itch, sneeze, and rhinorrhoea, while nasal blockage is vascular in origin and is determined predominantly by the direct action of mediators on the nasal blood vessels. A range of mediators has been related to the clinical expression of disease; namely, histamine, kinins, tryptase, PGs (particularly PGD_2), and LTs (particularly LTC_4 and LTD_4). Nasal challenge studies have been undertaken to explore the potential effects of these mediators.

Nasal insufflation with histamine produces a full range of nasal symptoms, including nasal blockage (76). The nasal itch, sneeze, and rhinorrhoea are completely abolished by H_1-receptor antagonists, indicative of the involvement of H_1-receptor stimulation. The nasal blockage is, however, only partially modified by H_1-antagonism. H_2-receptor antagonists can also modify the obstructive response; their effects with H_1-antihistamines are not additive, indicating that their protective effects are sequential in the same process (77). Thus, histamine-induced nasal blockage is incompletely modified by H_1- or H_2-receptor blockade, suggesting that histamine-mediated stimulation of H_3-receptors may also contribute (78). Nasal blockage is also induced by nasal insufflation with kinins, PGD_2, and LTC_4 and LTD_4. Thus, these mediators will also contribute to allergic disease. Nasal challenge with kinins induces a painful nasal sensation, different from histamine-induced itch, glandular secretion, and plasma protein extravasation (79). These effects are mediated through the kinin β2 receptor, as the β2 agonist kallidin, but not the β1 agonist [des-arg^9]-bradykinin, mimics the increase in nasal airways resistance and plasma protein exudation induced by bradykinin (80, 81). The effects of PGD_2, LTC_4, and LTD_4 are more limited, their predominant action being to induce nasal blockage. The LTs are also potent mediators of vascular permeability and induce plasma protein exudation (31). The effects of PGD_2 are mediated through a specific vascular receptor termed the DP receptor, as opposed to the common thromboxane (TP) receptor, through which PGD_2 exerts bronchorestrictor responses within the lower airways (82, 83). The cyst LT_1 receptor is most likely to be the vascular receptor responsible for the nasal effects of LTs.

Conclusions

Allergic rhinitis is an inflammatory nasal disorder in which a range of cells and mediators contribute, in a coordinated complex network that underlies clinical disease expression. Drug therapy is currently directed toward receptor antagonism of mediators, functional antagonism of end-organ responses, and inhibition of cell accumulation and/or activation. Histamine is a major contributor and, as such, receptor antagonists of the H_1-receptors have played a prominent role in management guidelines. Histamine is not, however, the only player, and this strategy will be only partially successful as sole therapy. Inhibition of other mediators is likely to confer additional benefit, and combination therapy with cyst LT_1-receptor antagonists and H_1-receptor antagonists has been tried. Alternatively, the development of drugs that have a broader profile of mediator antagonism/synthesis inhibition would similarly be expected to have a greater effect in improving symptoms. This has been sought with "antiallergic" antihistamines, drugs that block H_1-receptors and also either modify LT production or inhibit cell recruitment, thus decreasing the availability of activated eosinophils or basophils for the "mediator pool".

Acknowledgment

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